Understanding Australia's influenza pandemic policy on the strategic use of the antiviral drug stockpile

Published in final edited form as:
Med J Aust. 2009 August 3; 191(3): 136–137.

Understanding Australia's influenza pandemic policy on the strategic use of the antiviral drug stockpile:

Targeted post-exposure prophylaxis represents a more efficient use of the stockpile than treatment alone

James M McCaw, BSc, PhD[1][Research Fellow], James G Wood, BSc, PhD[2][Senior Lecturer], Emma S McBryde, MB BS, PhD, FRACP[3,4][Head of Epidemiology], Terry M Nolan, MB BS, PhD, FRACP[1][Head], Joseph T Wu, PhD[5][Assistant Professor], Marc Lipsitch, DPhil[6][Professor of Epidemiology], and **Jodie McVernon, BMedSc, MB BS, PhD[1][Deputy Head, and Program Leader, Mathematical Modelling]**

[1] Vaccine and Immunisation Research Group, Melbourne School of Population Health, University of Melbourne and Murdoch Childrens Research Institute, Melbourne, VIC

[2] School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW

[3] Victorian Infectious Diseases Service, Royal Melbourne Hospital, Melbourne, VIC

[4] Department of Medicine, University of Melbourne, Melbourne, VIC

[5] Department of Community Medicine and School of Public Health, University of Hong Kong, Hong Kong

[6] Department of Epidemiology and Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Mass, USA

With the emergence of H1N1 influenza 09 (novel human swine influenza A[H1N1] 2009), efforts to control the spread and mitigate the impact of this virus have been implemented. The *Australian health management plan for pandemic influenza (2008)*[1] (AHMPPI) outlines a range of strategies aimed at eliminating an outbreak where possible (the "Contain" response), or reducing transmission sufficiently to allow distribution of a targeted vaccine (the "Sustain" response). Following evidence of sustained transmission within Victoria in May 2009, state and territory health departments began implementing the Contain response, with a switch to a modified Sustain response in Victoria within weeks.

The AHMPPI recommends liberal distribution of the stockpile of neuraminidase inhibitors (oseltamivir, zanamivir) to constrain influenza transmission.[1] This policy was based on modelling studies synthesising the best available evidence, including clear demonstration of the efficacy of antiviral drugs to prevent secondary infection in randomised controlled trials.[2,3] Notwithstanding revision of the AHMPPI on 17 June 2009 to incorporate the present "Protect" phase, understanding the rationale for and defining the operational implications of the initial recommendations for antiviral drug use are priorities.

Correspondence: j.mcvernon@unimelb.edu.au.

Competing interests

Marc Lipsitch has received consulting fees from the Avian/Pandemic Flu Registry, which is partly supported by Roche.

Translation of evidence from epidemiological trials into pandemic policy is challenging, given the complexity of real-world factors that influence intervention effectiveness. For example, as has been observed with many vaccines, drug effects on transmission have far greater impact when implemented across a whole population. The chosen antiviral deployment strategy needs to take into account not only the direct effects benefiting the treated individual, but also indirect effects due to changes in subsequent transmission. In a rapidly growing epidemic, these secondary effects are critical to determining the optimal deployment strategy. Mathematical modelling provides a way to systematically investigate these issues.

Using a diverse set of assumptions and frameworks, models consistently demonstrate that for a country with a sufficiently large stockpile of antiviral drugs, augmenting a patient treatment policy with targeted post-exposure prophylaxis represents a more efficient use of the stockpile than treatment alone.[4–6] Modelling performed in the Australian context, where the number of stockpiled antiviral drug courses is 40% of the population size, has demonstrated that extensive drug distribution for preventive purposes does not compromise the ability to treat infected patients.[6] It was therefore recommended in the AHMPPI that prophylaxis should be provided to as many readily identifiable contacts as possible during the Contain response, with continued provision to household contacts during the Sustain response. Provision of continuous pre-exposure prophylaxis to health care workers was also recommended, as this additive burden on the stockpile would not substantially impede efforts to delay the pandemic.

Lessons learned so far in the effort to implement these recommendations have highlighted the importance of clear case definitions to guide treatment, particularly when disease is mild. Delays in confirming infection, associated with finite laboratory resources, posed significant challenges for front-line health care workers. This practical issue must be addressed should deployment of existing stockpile reserves be recommended in coming years, as potentially more virulent variants of the present pandemic strain arise.

Meanwhile, further research and policy development are required on a largely unaddressed issue. A transmissible drug-resistant variant of the pandemic strain may arise either by de-novo mutation or by reassortment with drug-resistant seasonal strains (eg, the oseltamivir-resistant 2008 seasonal H1N1 strain carrying the H274Y mutation [histidine-to-tyrosine mutation at codon 274]), and its spread would be favoured by widespread antiviral use. The effort to delay the appearance of such a variant might stimulate a change to the recommended strategies for antiviral deployment. To date, novel H1N1 viruses demonstrating oseltamivir resistance have been isolated from individuals in Denmark and Japan.[7]

Several published models have been used to investigate the potential consequences of antiviral drug resistance and all demonstrate that emergence of a transmissible drug-resistant variant will reduce the effectiveness of antiviral distribution strategies, with obvious consequences for their utility in “buying time” before a targeted vaccine becomes available. Two recent studies have investigated strategies for reducing the negative impact of drug resistance.[8,9] Both considered the case where the main stockpile (ie, oseltamivir) is supplemented with a smaller secondary stockpile of another drug (eg, zanamivir).

One study considered four strategies for antiviral drug distribution when both drugs are available for treatment and prophylaxis.[8] It was concluded that a strategy whereby the smaller stockpile (drug B) is reserved for treatment, while the main stockpile (drug A) is used for prophylaxis, will most effectively delay the peak of the epidemic and result in the lowest overall level of drug resistance. Alternative strategies of random allocation of drug A

or drug B to each individual who is prescribed an antiviral drug, or use of drug B followed by drug A, were also shown to have significant benefits over a single-drug policy. Cycling between one drug and the other over a period of weeks or months was shown to be a high-risk strategy and cannot be recommended.

Treatment strategies were also considered in the other study, which demonstrated that using a small amount of drug B followed by drug A will reduce the overall attack and greatly reduce the resistant attack rate.[9] In addition, the global implications of a two-drug strategy were considered, taking into account regular entry of infectious individuals into countries and regions over the course of a pandemic. It was shown that if the primary source country implements a strategic two-drug distribution policy, any country into which strains are subsequently introduced will gain a significant benefit from implementing a similar policy.

Both these studies provide strong evidence for jurisdictions to consider acquisition of a secondary drug to supplement their primary drug stockpile. Whether the stockpiles are deployed in order (drug B, then drug A) or separated for use as treatment only and prophylaxis only would largely depend on logistical constraints and overall feasibility of the alternative strategies. Either strategy is likely to provide significant benefits compared with deployment of a single drug.

In a climate of great uncertainty surrounding characteristics of the current influenza outbreak,[10] the challenge worldwide is for jurisdictions to implement flexible evidence-based policies for antiviral stockpile distribution that maximise their effectiveness.

Acknowledgments

We thank Julie Hall (World Health Organization Regional Office for the Western Pacific), Niels Becker (National Centre for Epidemiology and Population Health, Australian National University), John Mathews, Chris McCaw and Paul Pallaghy (Melbourne School of Population Health, University of Melbourne) for discussions and comments during development of the modelling approaches that underpin this article, and members of the Scientific Influenza Advisory Group of the Chief Medical Officer of Australia for their comments. The outlined modelling studies were funded by the Australian Government Department of Health and Ageing, the National Health and Medical Research Council (NHMRC) and the United States National Institutes of Health (Models of Infectious Disease Agent Study).

References

1. Australian Government Department of Health and Ageing. Australian health management plan for pandemic influenza (2008). Canberra: DoHA; 2008. http://www.flupandemic.gov.au/internet/panflu/publish-ing.nsf/Content/ahmppi
2. Becker, NG.; Glass, K.; Barnes, B., et al. Final report to the Australian Government Department of Health and Ageing. Canberra: National Centre for Epidemiology and Population Health, Australian National University; 2006. Using mathematical models to assess responses to an outbreak of an emerged viral respiratory disease.
3. Halloran ME, Hayden FG, Yang Y, et al. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. Am J Epidemiol. 2007; 165:212–221. [PubMed: 17088311]
4. Ferguson NM, Cummings DAT, Fraser C, et al. Strategies for mitigating an influenza pandemic. Nature. 2006; 442:448–452. [PubMed: 16642006]
5. Longini I, Nizam A, Xu S, et al. Containing pandemic influenza at the source. Science. 2005; 309:1083–1087. [PubMed: 16079251]
6. McCaw JM, McVernon J. Prophylaxis or treatment? Optimal use of an antiviral stockpile during an influenza pandemic. Math Biosci. 2007; 209:336–360. [PubMed: 17416393]
7. International Society for Infectious Diseases. ProMED-mail Archive Number 20090630.2359. PRO/AH/EDR> Influenza A (H1N1) - worldwide (78): Tamiflu resistance, DK. Jun 30. 2009 http://www.promedmail.org/pls/otn/f?

p=2400:1001:3406131671527906::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1004,78150

8. McCaw JM, Wood JG, McCaw CT, McVernon J. Impact of emerging antiviral drug resistance on influenza containment and spread: influence of subclinical infection and strategic use of a stockpile containing one or two drugs. PLoS One. 2008; 3:e2362. [PubMed: 18523549]
9. Wu JT, Leung GM, Lipsitch M, et al. Hedging against antiviral resistance during the next influenza pandemic using small stockpiles of an alternative chemotherapy. PLoS Med. 2009; 6:e1000085. [PubMed: 19440354]
10. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science. 2009; 324:1557–1561. [PubMed: 19433588]